

1 BIOPSY SITE MARKER AND PROCESS AND APPARATUS FOR
2 APPLYING IT

BACKGROUND OF THE INVENTION

4 1. Field of the Invention

5 The present invention is in the field of markers to be employed at
6 biopsy sites to permanently mark the site, and to methods and apparatus for
7 applying the permanent marker. More particularly, the present invention
8 relates to a marker that is optimally adapted for marking biopsy sites in human
9 breast tissue with permanently placed markers that are detectable by X-ray.

10.2. Brief Description of the Background Art

11 In modern medical practice small tissue samples, known as biopsy
12 specimens, are often removed from tumors, lesions, organs, muscles and other
13 tissues of the body. The removal of tissue samples may be accomplished by
14 open surgical technique, or through the use of a specialized biopsy
15 instruments such as a biopsy needle. A well known state-of-the-art instrument
16 that is often used in connection with the practice of the present invention is
17 known as the "vacuum assisted large core biopsy device".

18 After a tissue sample has been removed, it is typically subjected to
19 diagnostic tests or examinations to determine cytology, histology, presence or
20 absence of chemical substances that act as indicators for disease states, or the
21 presence of bacteria or other microbes. The above mentioned and other
22 diagnostic tests and examinations *per se* are well known in the art and need
23 not be described here. It is sufficient to note that the information obtained
24 from these diagnostic tests and/or examinations is often of vital importance
25 for the well-being of the patient and is used to make or confirm diagnoses and
26 often to formulate treatment plans for the patient. As is known, obtaining a
27 tissue sample by biopsy and the subsequent examination are frequently,
28 almost invariably, employed in the diagnosis of cancers and other malignant
29 tumors, or to confirm that a suspected lesion or tumor is not malignant, and

1 are frequently used to devise a plan for the appropriate surgical procedure or
2 other course of treatment.

3 Examination of tissue samples taken by biopsy, often by the above-
4 mentioned "vacuum assisted large core biopsy sampler" is of particular
5 significance in the diagnosis and treatment of breast cancer which is the most
6 common cancer suffered by women in the U.S.A and elsewhere in the
7 industrially developed world. Proper diagnostic procedures, frequent
8 examination by well known techniques such as "mammography" and prompt
9 subsequent surgical treatment have, however, significantly reduced the
10 mortality rate caused by this form of cancer. For this reason, in the ensuing
11 discussion of the pertinent background art and in the ensuing description the
12 invention will be described as used for marking biopsy sites in human and
13 other mammalian breast, although the invention is suitable for marking biopsy
14 sites in other parts of the human and other mammalian body as well.

15 Thus, as is known, when an abnormal mass in the breast is found by
16 physical examination or mammography a biopsy procedure follows almost
17 invariably. The nature of the biopsy procedure depends on several factors.
18 Generally speaking, if a solid mass or lesion in the breast is large enough to be
19 palpable (i.e., felt by probing with the fingertips) then a tissue specimen can
20 be removed from the mass by a variety of techniques, including but not
21 limited to open surgical biopsy or a technique known as Fine Needle
22 Aspiration Biopsy (FNAB). In open surgical biopsy, an incision is made and
23 a quantity of tissue is removed from the mass for subsequent histopathological
24 examination. In the FNAB procedure, a small sample of cells is aspirated
25 from the mass through a needle and the aspirated cells are then subjected to
26 cytological examination.

27 If a solid mass of the breast is small and non-palpable (e.g., the type
28 typically discovered through mammography), a relatively new biopsy
29 procedure known as "stereotactic needle biopsy" may be used. In performing

1 a stereotactic needle biopsy of a breast, the patient lies on a special biopsy
2 table with her breast compressed between the plates of a mammography
3 apparatus and two separate digital x-rays are taken from two slightly different
4 points of view. A computer calculates the exact position of the lesion with X
5 and Y coordinates as well as depth of the lesion within the breast. Thereafter,
6 a mechanical stereotactic apparatus is programed with the coordinates and
7 depth information calculated by the computer, and such apparatus is used to
8 precisely advance the biopsy needle into the small lesion. Usually at least five
9 separate biopsy specimens are obtained from locations around the small lesion
10 as well as one from the center of the lesion.

11 After the biopsy sample is taken, it may take several days or even a
12 week before the results of the examination of the sample are obtained, and
13 still longer before an appropriate treatment decision is reached. If the decision
14 involves surgery it is clearly important for the surgeon to find the location in
15 the breast from where the tumor tissue has been taken in the biopsy procedure,
16 so that the entire tumor and possibly surrounding healthy tissue can be
17 removed. For example, the particular treatment plan for a given patient may
18 require the surgeon to remove the tumor tissue and 1 centimeter of the tissue
19 surrounding the tumor. A co-pending application for United States Letters
20 Patent by the same inventors discloses markers which are particularly well
21 adapted for marking biopsy sites in the human breast, and which markers
22 remain detectable by X-ray, ultrasound or some other detection technique only
23 for a given time period (*i. e.* for 6 months) and slowly disappear thereafter, for
24 example by absorption into the body. The purpose of such markers is to
25 facilitate the surgical procedure that is performed while the marker is still
26 detectable. The disappearance of the marker after a longer period of time may
27 be advantageous to avoid obscuring or interfering with follow-up studies or
28 further mammography or other imaging studies.

29 In connection with the background art the following specific printed art

1 is mentioned. United States Patent Nos. 2, 192, 270 and 5, 147, 307 describe
2 visually discernible markers that are applied externally to the patient's skin.
3 Radiographically (X-ray) detectable tissue markers (e.g., clips or staples) that
4 are attached to tissue adjacent to the site from which the biopsy specimen has
5 been removed, are described in International Patent Publication No. WO
6 98/06346. Radiographically visible markers (*e. g.* marker wires) that may be
7 introduced into the biopsy site and are inserted through the biopsy needle after
8 a tissue sample is removed and which are thereafter allowed to remain
9 protruding from the patient's body, are also described in WO 98/06346.
10 However, due to the consistency of breast tissue and the fact that these biopsy
11 site markers are typically introduced while the breast is still compressed
12 between the mammography plates, these biopsy markers of the prior art may
13 become attached to adjacent bands of connective tissue that do not remain at
14 the specific location of the biopsy after the breast has been decompressed and
15 removed from the mammography apparatus, and may suffer from additional
16 disadvantages as well.

17 Thus, there is still a need in the art for of biopsy site markers that are
18 deliverable into the cavity created by removal of the biopsy specimen and not
19 into tissue that is located outside of that biopsy cavity, and which will not
20 migrate from the biopsy cavity even when the breast tissue is moved,
21 manipulated or decompressed. Moreover, such desired markers should
22 remain detectable at the biopsy site *i. e.* within the biopsy cavity for an
23 indefinite time period, and still should not interfere with imaging of the
24 biopsy site and adjacent tissues at a later point of time, and most importantly
25 should be readily distinguishable in the various imaging procedures from lines
26 of calcifications which frequently are signs for a developing malignancy. The
27 present invention provides such permanent biopsy site markers as well as
28 apparatus and method for delivering such markers into the biopsy cavity.

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SUMMARY OF THE INVENTION

2 It is an object of the present invention to provide a biopsy site marker
3 that is deliverable into the cavity created by removal of the biopsy specimen.

4 It is another object of the present invention to provide a biopsy site
5 marker that does not migrate from the biopsy cavity even when the
6 surrounding tissue is moved, manipulated or decompressed.

7 It is still another object of the present invention to provide a biopsy site
8 marker that meets the foregoing requirements and that remains detectable at
9 the biopsy site for an indefinite period of time.

10 It is yet another object of the present invention to provide a biopsy site
11 marker that meets the foregoing requirements and that is readily
12 distinguishable by X-ray from granules or lines of calcifications which
13 frequently are signs for a developing malignancy.

14 It is a further object of the present invention to provide an apparatus
15 and method for placing into the biopsy cavity a biopsy site marker that meets
16 the foregoing requirements.

17 These and other objects and advantages are attained by a biopsy site
18 marker that comprises small bodies or pellets of gelatin which enclose
19 substantially in their interior a radio (X-ray) opaque object. The gelatin
20 pellets are deposited into the biopsy site, typically a cylindrical opening in the
21 tissue created by the recent use of a vacuum assisted large core biopsy device,
22 by injection from an applicator through a tube that is placed into the biopsy
23 site. Typically, several gelatin pellets, only some of which typically do, but
24 all of which may contain the radio opaque object, are deposited sequentially
25 from the applicator into the site through the tube. The radio opaque objects
26 contained in the gelatin bodies have a non-biological shape or configuration
27 to be identifiable as a man-made object such that in observation by typical
28 mammography equipment, that is when viewed from at least two different
29 viewing angles, they do not assume the shape of a line, whereby they are

1 readily distinguishable from granules or lines of calcification.

2 The features of the present invention can be best understood together
3 with further objects and advantages by reference to the following description,
4 taken in connection with the accompanying drawings, wherein like numerals
5 indicate like parts.

6 **BRIEF DESCRIPTION OF THE DRAWINGS**

7 **Figure 1** is a perspective view of a preferred embodiment of the biopsy
8 site marker of the present invention.

9 **Figure 2** is a perspective view of a plurality of biopsy site markers in
10 accordance with the first embodiment of the present invention.

11 **Figure 3** is a perspective view of an applicator apparatus in accordance
12 with the present invention, for depositing the biopsy site marker at a biopsy
13 site.

14 **Figure 4** is a perspective view of the applicator apparatus of Figure 3,
15 showing the applicator with an extended piston indicating that the applicator
16 is loaded with biopsy site markers.

17 **Figure 5** is a cross-sectional view of the site marker shown in Figure 4,
18 the cross section taken on lines 5,5 of Figure 4.

19 **Figure 6** is an enlarged cross sectional view showing the applicator of
20 Figure 4 loaded with biopsy site markers in accordance with the present
21 invention.

22 **Figure 7** is a schematic view of a human breast, showing a biopsy
23 cavity of the type obtained by a vacuum assisted large core biopsy sampler,
24 into which a plurality of biopsy markers are deposited in accordance with the
25 present invention.

26 **DESCRIPTION OF THE PREFERRED EMBODIMENTS**

27 The following specification taken in conjunction with the drawings
28 sets forth the preferred embodiments of the present invention. The
29 embodiments of the invention disclosed herein are the best modes

1 contemplated by the inventors for carrying out their invention in a commercial
2 environment, although it should be understood that various modifications can
3 be accomplished within the parameters of the present invention.

4 Referring now to the drawing figures and particularly to **Figures 1** and
5 **2**, a body **20** of gelatin or reconstituted collagen in the shape of a pellet that
6 includes or incorporates a radio-opaque marker **22** of a definite shape is
7 disclosed. The gelatin or reconstituted collagen body **20** can be of virtually
8 any shape or configuration, however the herein shown shape of a cylinder or
9 pellet is preferred. The gelatin body of pellet **20** is of such size that several of
10 the pellets can be deposited in a biopsy site, such as a typical biopsy site
11 obtained by using the vacuum assisted large core biopsy device that is
12 frequently used in current medical practice. The gelatin body or pellet **20** is
13 stored and is applied, that is deposited in the biopsy site, in a dehydrated form
14 through an applicator device that forms another aspect of this invention.
15 However, when the gelatin body or pellet **20** of the invention is not deposited
16 through the applicator device, it does not necessarily need to be stored and
17 applied in a dehydrated form. Nevertheless, storing the gelatin pellets **20** in
18 dehydrated form increases their useful shelf-life and renders it easier to keep
19 them sterile.

20 After having been deposited at the biopsy site the gelatin marker **20**
21 slowly absorbs moisture from the surrounding tissue and becomes hydrated.
22 In the dehydrated form, shown in the appended drawing figures, the gelatin
23 body or pellet **20** is approximately 1 to 3 mm in diameter and is approximately
24 5 to 10 mm long. The presently preferred embodiment of the gelatin pellet **20**
25 is approximately 2 mm in diameter and is approximately 8 mm long. After
26 the pellet **20** has reached hydration equilibrium with the surrounding tissue it
27 becomes approximately 3 to 5 mm in diameter and approximately 10 to 15
28 mm long. After hydration the presently preferred embodiment of the pellet **20**
29 is approximately 4 mm in diameter and approximately 10 mm long.

1 The gelatin or reconstituted collagen material itself is observed under
2 ultrasound examination as a white spot because of the air pockets usually
3 entrapped in its matrix. In mammography the gelatin is observed as dark
4 spots in normal breast, because of the presence of the air pockets. In a fatty
5 breast viewed by mammography the gelatin marker is observed as a lighter
6 area containing dark spots, due to the water in the hydrated gelatin absorbing
7 more energy than the surrounding matrix and the air pockets within the
8 matrix. A pellet **20** or plurality of pellets **20** due to their bulk may also be
9 palpable and locatable by tactile means within the breast tissue or other tissue.
10 The gelatin or reconstituted collagen marker itself can be made even more
11 radio-opaque by ion-impregnation and chelation techniques which are
12 described in detail in the aforesaid co-pending application serial number
13 09/241,936 filed on February 2, 1999 by the same inventors in connection
14 with the description of biopsy markers of that application, and the description
15 of this method of rendering the gelatin markers radio-opaque is also provided
16 here below. The disclosure of co-pending application serial number
17 09/241,936 is incorporated herein by reference in its entirety. The gelatin or
18 reconstituted collagen material can also be made more radio-translucent by
19 entrapping (mixing) a substantial amount of air in the gelatin. Moreover, a
20 visually detectable substance, such as carbon particles, or a suitable dye (e. g.
21 methylene blue or indigo) may also be added to the gelatin to make the marker
22 visible by a surgeon during dissection of the surrounding breast tissue.

23 The gelatin or reconstituted collagen *per se* does not serve as a
24 permanent marker of the biopsy site because it is eventually reabsorbed by the
25 body, although the dye or even ionic material that made the gelatin visible or
26 radio-opaque, respectively, may remain at the site for longer time period than
27 the palpable gelatin pellet, and may remain there indefinitely. Factors which
28 influence how long the gelatin or reconstituted collagen pellet remains at the
29 site, and various means to adjust this time period are described in the afore-

1 mentioned co-pending application serial number 09/241,936.

2 It is a novel and important aspect of the present invention to
3 incorporate into the gelatin or reconstituted collagen body or pellet 20 the
4 radio-opaque marker 22. The radio-opaque or X-ray detectable marker 22
5 that is incorporated or enclosed in the gelatin pellet 20 must have the
6 following properties. First, by its very nature it must be detectable by X-ray,
7 including the type of radiography used in the practice of mammography. It
8 must be comprised of a material or composition that is not absorbed by the
9 body and stays for indefinite time at the biopsy site, retains its shape and
10 remains X-ray detectable at the biopsy site also for an indefinite time. The
11 material or composition of the radio-opaque marker 22 must, of course, be
12 biocompatible at the site where it is deposited. Another important
13 requirement is that the biocompatible marker must have an identifiable
14 specific non-biological shape or form. The purpose of specific form for the
15 marker is to render the marker distinguishable under X-ray or in a
16 mammographic examination from naturally formed calcification granules or a
17 line of such granules, which are also X-ray opaque. As is known, a line of
18 calcification which normally forms along ducts is considered a sign of
19 developing malignancy. Thus, the marker 22 should be of such specific
20 configuration that when it is viewed sterically, as during a mammography
21 examination, it should be distinguishable from an X-ray opaque line.
22 Numerous specific shapes or configurations satisfy the foregoing
23 requirements, however amorphous X-ray opaque material that would be
24 uniformly (or substantially uniformly) distributed in the gelatin pellet 20 is
25 unlikely to satisfy these requirements.

26 Materials or compositions which are suitable for the marker 22 include
27 metal, such as stainless steel, tantalum, titanium, gold, platinum, palladium,
28 various alloys that are normally used in bioprostheses and ceramics and metal
29 oxides that can be compressed into specific shapes or configurations. Among

1 these the use of biocompatible metals is presently preferred, and the herein
2 described preferred embodiment of the marker 22 is made of stainless steel.
3 Generally speaking the marker 22 is approximately 0.010 to 0.060 inches
4 wide, approximately 0.030 to 0.200 " long and approximately 0.002 to 0.020 "
5 thick. The presently preferred permanent marker 22 shown in the drawing
6 figures has the configuration or shape approximating an upside down turned
7 Greek letter gamma (γ), is approximately 0.10" long and approximately 0.040
8 " wide. The upside-down Greek letter gamma (γ) shape is believed to be
9 unique, has some resemblance to the popular breast cancer awareness ribbon
10 and is readily distinguishable under X-ray and mammography as a "man-
11 made" marker object from any naturally formed X-ray opaque body. Various
12 manufacturing techniques which *per se* are well known in the art, can be
13 utilized to manufacture the X-ray opaque permanent marker 22. Thus, the
14 marker 22 can be formed from wire, or can be electrochemically etched or
15 laser cut from metal plates. The presently preferred embodiment of the
16 gamma (γ) shaped marker 22 is formed by electrochemical etching from
17 stainless steel plates.

18 **Figures 1, 2** and the other drawing figures, as applicable, show only
19 one marker in the gelatin pellet 20, although more than marker may be
20 incorporated in the pellet 20. **Figure 1** discloses a cylindrically shaped gelatin
21 pellet 20 that in accordance with the present invention includes the gamma
22 (γ) shaped stainless marker 22, and as an optional feature also includes a dye
23 or other coloring material (e. g. indigo) that also stays substantially
24 permanently at the biopsy site and is visible by a surgeon when the breast
25 tissue is dissected, as in an operation where tumor tissue is removed
26 (lumpectomy).
27 Gelatin bodies or pellets 20 all of which include one or more permanent radio
28 opaque markers 22 in accordance with the present invention may be deposited

1 at a biopsy site. Alternatively, a series of gelatin bodies or pellets **20** where
2 only some but not all include a permanent X-ray opaque marker **22** of unique
3 non-biological shape, may be deposited at the biopsy site. Preferably, a series
4 of pellets **20** are deposited where each second, each third, or each fourth etc.,
5 pellet includes the marker **22**. **Figure 2** discloses an example of a series or
6 sequence of pellets **20** where each second pellet **20** includes the metal marker
7 **22** and where each pellet **20** that does not include the metal marker **22**
8 includes carbon black or dye that is visible to the surgeon during operation.
9 In this connection it should be understood and appreciated that as noted above
10 the gelatin bodies or pellets **20** themselves serve a purpose of marking the
11 biopsy site for a predetermined length of time, that is until they become
12 absorbed by the body.

13 The drawing figures, particularly **Figures 1** and **2** show the metal
14 marker **22** disposed substantially in the center of the cylindrical gelatin pellet
15 **20**. This is preferred but is not necessary for the present invention. The
16 metal marker **22** can be embodied in or included in the gelatin body **20**
17 virtually anywhere. The gelatin body or pellet **20** however has to have
18 sufficient integrity or firmness to retain the metal marker **22** and air bubbles
19 which are usually deliberately entrapped in the gelatin. As is known, the
20 firmness or bodily integrity of gelatin is measured in units of Bloom.
21 Generally speaking it was found in accordance with the present invention that
22 the higher the Bloom strength of the gelatin used in the marker **20** the better
23 the marker performs. The higher Bloom strength gelatin holds gas bubbles
24 within its matrix better than lower Bloom strength gelatin. Gelatin with a
25 Bloom strength of approximately 150 especially 175 is adequate for the
26 practice of the present invention, but a more preferred range is 200 to 300
27 Bloom, the most preferred range being between 250 and 300. (For
28 comparison, typical food gelatin is approximately 75 Bloom, and gelatin of
29 300 Bloom feels like a soft rubber eraser.)

1 A description how to obtain gelatin or reconstituted collagen bodies
2 suitable for use as markers 20 with various properties, before the permanent
3 radio-opaque metal or like marker 22 of specific form is incorporated therein,
4 is provided below in connection with following examples.

5 Example of Radiographically Visible/Palpable Marker Material Formed
6 of Metal Ions In Combination With a Collagenous or Gelatinous Matrix

7 United States Patent No. 4,847,049 (Yamamoto incorporated herein by
8 reference) describes an ion-impregnation or chelation technique whereby an
9 ion may be impregnated or chelated to collagen for the purpose of imparting
10 antimicrobial properties to the collagen preparation. Thus, using this
11 technique, imageable ions such as radiographically visible metal ions, may be
12 bound to a bulky collagenous material to form a marker 10 that may be a)
13 imaged by radiographic means and b) located by palpation of tissue
14 surrounding the biopsy site. For example, a silver ion-renatured collagen
15 composition may be prepared by the following process:

16 Step 1-Renaturation of Collagen (or Gelatin):

17 Collagen may be renatured to an insoluble form by processing of
18 denatured collagen that has been obtained from a natural source such as
19 bovine corium (hide), bovine tendon, and porcine skin. Alternatively, pre-
20 processed, insoluble collagen may be purchased in the form of a commercially
21 available hemostatic material such as CollastatTM and AviteneTM nonwoven
22 web. Methods for renaturing collagen are known in the literature, including,
23 for example, those methods described in United States Patent Nos. 4,294,241
24 and 3,823,212. The specifications of United States Patent Nos. 4,294,241 and
25 3,823,212 are incorporated herein by reference.

26 A particularly preferred form of renatured collagen for utilization in
27 accordance with the present invention is one that has been renatured *and*
28 covalently cross-linked. This collagen may be prepared by utilizing readily
29 available polyfunctional cross linking agents or fixatives, such as dialdehydes,

1 dicarboxylic acids, diamines, and the like. Typically, tropocollagen is
2 dissolved in a buffer of pH 3.0 to 5.0 to provide a solution containing
3 approximately 1 to 2% by weight of the collagen. Then 1% of a dialdehyde
4 cross-linking agent such as glutaraldehyde or formaldehyde is then added.
5 The mixture is then frozen and stored for approximately 24 hours. After
6 thawing and washing to remove unreacted cross linking agent, the renatured
7 cross-linked collagen is then ready for contact with a silver ion-containing
8 solution.

9 Step 2-Binding of Metal Ions to the Renatured Collagen:

10 The source of silver ion may be a water soluble silver salt, preferably
11 silver nitrate. While the concentration of the silver ion in the solution is not
12 particularly critical, it will be usually convenient to utilize solutions in the
13 concentration range of about 10 to 10 millimolar.

14 The renatured collagen is preferably contacted with a silver ion-
15 containing solution in the pH range of about 4 to 9. The pH of the silver ion-
16 containing solution can be controlled by the addition of an appropriate
17 titrating agent, such as nitric acid, or potassium hydroxide, as required, to
18 maintain the pH at less than about 9.0 to avoid the degradation of the silver.
19 There is not believed to be any lower limit for the pH, however, normally a
20 pH above 4.0 will be convenient. A particularly preferred range for the pH is
21 from 7.0 to 7.5. The binding capacity of silver by collagen is particularly
22 effective within this preferred pH range, although the amount of binding by
23 silver by the collagen is further controllable by the concentration of the silver
24 ion-containing solution and/or exposure time of the collagen to the silver ion-
25 containing solution. Simultaneous with or subsequent to exposure of the
26 collagen to the silver ion-containing solution, the collagen is then exposed to
27 ultraviolet radiation of energy and duration sufficient to strengthen the
28 binding of the silver ions to the collagen without substantial formation of
29 metallic silver formed as a result of oxidation of various functional groups in

1 the collagen by the silver ion. While the exact limits of the ranges of the
2 conditions which will be sufficient to strengthen the binding of the silver ions
3 without substantial formation of metallic silver are not precisely determinable,
4 it will generally suffice to maintain the pH of the silver-collagen environment
5 at less than 8.0 while exposing the collagen to ultraviolet radiation in the
6 range of about 210 to 310 nm wavelength for about from 5 to 15 minutes. The
7 time of UV exposure for complete reaction is inversely proportional to the
8 light intensity which is preferably in the range of 100 to 1,000
9 microwatts/cm². A slight coloration of the collagen due to the exposure to
10 ultraviolet radiation is acceptable, i.e., a turning from white to a light brown to
11 yellow color, indicating a slight oxidation reaction occurring in the collagen,
12 however, the radiation should not be to the extent that dark brown or black
13 areas in the collagen occur due to over-oxidation and/or substantial formation
14 of metallic silver. Normally the exposure will be performed at ambient
15 temperatures, i.e., in the range of about 20 degrees to 25 degrees C, however,
16 there is not believed to be any reason why the exposure could not occur at
17 higher or lower temperatures providing that the temperature is not high
18 enough to cause degradation of the collagen and/or silver ion. There is not
19 believed to be any lower limit to the temperature at which the exposure may
20 take place, provided it is above the freezing point of the ion-containing
21 solution.

22 Ultraviolet radiation may be provided by any conventional ultraviolet
23 radiation source of appropriate wavelength, such as germicidal lamps and
24 mercury/xenon lamps.

25 Step 3 (optional)-Addition of Visible Marker Component to the
26 Collagen or Gelatin Matrix:

27 If it is desired for the marker to be detectable visually, as well as by
28 imaging and palpation, a quantity of a visible substance having a color
29 dissimilar blood or tissue may be added. For example, carbon particles or a

1 dye (e.g., methylene blue, indigo) may be added to the above-prepared silver
2 ion/collagen preparation to provide a colored silver ion/collagen marker 10
3 that is imageable (by radiographic means), palpable (by hand) and visible
4 (under white light in the operating room).

5 The above-described collagen-metal ion marker 10 (with or without
6 visible marker component) is introduced into the cavity created by removal of
7 the biopsy specimen. The quantity of this marker 10 introduced may be
8 sufficient to distend or stretch the biopsy cavity somewhat, thereby creating a
9 more palpable and obvious mass of marker material at the biopsy site.

10 Renatured gelatin or a cross-linked gelatin preparation such as
11 GelfoamTM may be impregnated or combined with a metal ion to provide a
12 gelatin-metal ion marker material. The gelatin may be prepared and ion-
13 bound by the same method as set forth hereabove for collagen.

14 Example of Radiographically or Ultrasonically Visible/Palpable Marker
15 Material Formed of a Gas in Combination With a Collagenous or
16 Gelatinous Matrix

17 Step 1-Renaturation of Collagen (or Gelatin):

18 Collagen or gelatin is renatured, as by the method described in Step 1
19 of the immediately preceding example and described in the literature,
20 including, for example, those methods described in United States Patent Nos.
21 4,294,241 and 3,823,212.

22 Step 2-Dispersing of Air or Other Gas in the Renatured Collagen or Gelatin
23 Matrix

24 Air or another biologically inert gas (e.g., carbon dioxide) is then
25 dispersed throughout the renatured collagen or gelatin matrix by a suitable
26 means such as mixing, mechanical blending, nucleation, bubbling, etc. This
27 results in the formation of many small gas bubbles throughout the collagenous
28 or gelatinous matrix and provides a marker substance that can be introduced
29 into the biopsy cavity through a cannula or tube and is substantially more

1 radio-lucent than the tissue surrounding the biopsy cavity. In this regard, this
2 marker can be imaged by x-ray *or* ultrasound but will not block or obscure
3 imaging of tissue that lies immediately adjacent the biopsy cavity. Also,
4 because of the bulk of the collagen or gelatin matrix, the marker is readily
5 palpable and locatable by tactile means within the surrounding breast tissue or
6 other tissue.

7 Step 3 (optional)-Addition of Visible Marker Component:

8 If it is desired for the marker to be detectable visually, as well as by
9 imaging and palpation, a quantity of a visible substance having a color
10 dissimilar to blood or tissue may be added. For example, carbon particles or a
11 dye (e.g., methylene blue, indigo) may be added to the above-prepared silver
12 ion/collagen preparation to provide a colored silver ion/collagen marker 10
13 that is imageable (by radiographic means), palpable (by hand) and visible
14 (under white light in the operating room).

15 In routine use, the above-described collagen/gas or gelatin/gas marker
16 10 (with or without visible marker component) is introduced into the cavity
17 created by removal of the biopsy specimen. The quantity of this marker 10
18 introduced may be sufficient to distend or stretch the biopsy cavity somewhat,
19 thereby creating a more palpable and obvious mass of marker material at the
20 biopsy site.

21 Preferred Example of Preparing Cylindrically Shaped Gelatin Pellets **20**
22 Having a Colorant and Including the Permanent Marker **22**

23 80 grams of dry gelatin obtained from porcine skin is mixed into 1000
24 ml of hot water (180 °F). Variations in gelatin to water ratio will change the
25 consistency but are nevertheless permissible within the scope of the invention.
26 The 80 grams of gelatin is about the maximum amount which will dissolve in
27 water without modifications to pH. The gelatin is then fully dissolved in the
28 water with slight mixing. In a separate container, 1.6 grams of indigo
29 colorant is mixed into 20 ml of ethyl alcohol. Then the ethanol solution of the

1 colorant is added by mixing to gelatin dissolved in water. Air is then
2 whipped into gelatin mixture to froth the mixture .

3 The gelatin dissolved in water is then poured into molds (not shown)
4 which have the shape of the desired gelatin body. In the preferred
5 embodiment the mold is shaped to provide the cylindrical pellet shown in the
6 drawing figures. One gamma (γ) shaped permanent marker 22, made by
7 chemical etching from stainless steel plates, is deposited into the gelatin in
8 each mold. (In alternative embodiments more than one marker 22 may be
9 deposited into each mold.) Due to the viscosity of the gelatin solution the
10 marker 22 does not usually sink to the bottom of the mold. The top of the
11 plate (not shown) holding a plurality of molds is squeegeed to level the
12 mixture.

13 After cooling to approximately 40 ° F or cooler temperature the gelatin
14 sets and provides the gelatin body 20 that incorporates the permanent marker
15 22 However, in order to dehydrate the marker it is first frozen and thereafter
16 lyophilized in commercial lyophilization apparatus. Gelatin pellets containing
17 the permanent marker 22 but not having a colorant can be prepared in the
18 same manner, but without adding indigo dye or other colorant. Gelatin bodies
19 or markers 20 that do not include or incorporate a permanent marker 22 can
20 also be made in this manner, but without depositing the marker 22 into the
21 gelatin after it has been placed into the mold. The gelatin body 20 prepared in
22 this manner is reabsorbed from the biopsy site by the human body in
23 approximately three weeks, whereas the permanent marker 22 remains
24 indefinitely.

25 Description of the Applicator Apparatus and its Use in Conjunction with
26 the Biopsy Marker of the Invention

27 Referring now to Figures 3 - 7 the applicator device or apparatus 24
28 with which the biopsy markers of the invention are preferably applied or
29 deposited, is disclosed. In this connection it should be understood that the

1 biopsy markers of the invention can be used without the applicator, and can be
2 deposited in accordance with the various methods and techniques utilized in
3 the state-of-the-art. However, a preferred technique of applying the biopsy
4 markers of the invention is to place or deposit them in a biopsy cavity that is
5 obtained with a vacuum assisted large core biopsy device of the type presently
6 used in the state-of-the-art. Such a device, distributed for example by Johnson
7 and Johnson Endo Surgery is well known in the art, and is schematically
8 shown in **Figure 7**.

9 The applicator 24 of the invention comprises an elongated cylindrical
10 body 26 having an interior cavity and a piston 28 that fits and slides back and
11 forth in the elongated cylindrical body 26. The cylindrical body 26 has an
12 enlarged disk 30 at one end 32. The disk 30 serves to render it convenient for
13 a user (not shown) to operate the applicator 24, as is described below. The
14 cylindrical body 26 that can also be described as an elongated flexible tube
15 has an opening 34 that commences a relatively short distance, that is
16 approximately 0.3 " before its other, closed end 36. The opening 34 is
17 configured to form a ramp in the side of the tube 26. The outer diameter of
18 the tube 26 is such that it fits through the vacuum assisted large core biopsy
19 device 38 shown in **Figure 7**. In this connection it should of course be
20 understood that the precise dimensions of the tube 26 are coordinated with the
21 dimensions of the piston 28 and with the vacuum assisted large core biopsy
22 device 38. Moreover, the diameter of the gelatin pellets 20 in their
23 dehydrated form are also coordinated with the inner diameter of the cylinder
24 or tube 26. The cylinder or tube 26 and the piston 28 can be made from any
25 appropriate medical grade plastic material, and is preferably made of high
26 density polyethylene. The outer diameter of the presently preferred
27 embodiment of the cylinder or tube 26 is approximately 0.093 " and its inner
28 diameter is approximately 0.070 ".

29 In the preferred manner of using the biopsy markers of the present

1 invention having the permanent markers 22 incorporated in a gelatin body 20,
2 as well as using biopsy markers that have only the gelatin body 20 without a
3 permanent marker 22, the applicator device 24, more precisely the tube 26 is
4 loaded with a desired number of pellets 20, as is shown in **Figures 4 - 6**. Any
5 number of pellets 20 within the range of 1 to approximately 30 may be loaded
6 within the tube 26, however presently it appears that approximately 8 pellets
7 20 are optimal for being loaded into the tube 26 and to be deposited in a
8 biopsy cavity where approximately 1 gram of tissue had been removed. Such
9 a biopsy cavity 40 in a human breast 42 is schematically illustrated in **Figure**
10 7. The pellets 20 which are loaded into the applicator tube 26 may all include
11 the permanent marker 22, but it is presently preferred that only every other
12 pellet 20 loaded into the applicator tube 26 have the permanent marker 22.
13 Such an array of 8 pellets 20, alternating between pellets with and without
14 permanent markers 22 is shown in **Figure 2**.

15 When the pellets 20 are in the tube 26 the piston 28 is extended, as is
16 shown in **Figures 4 and 5**. The pellets 20 are expelled one-by-one from the
17 tube 26 through the ramp-shaped opening 34 as the piston 28 is pushed into
18 the cylinder or tube 26. During this process the closed end 36 of the tube 26
19 is disposed in the cavity 40 formed by biopsy sampling. It is contemplated
20 that the dispersed radio-opaque permanent markers 22 provide a good
21 definition of the entire biopsy cavity 40 for subsequent observation or surgical
22 procedure. **Figure 3** illustrates the applicator device 24 after the pellets 20
23 have been expelled from the applicator tube 26.